Ethical and practical issues with opioids in life-limiting illness

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Effective pain relief, especially at the end of life, is a primary ethical obligation based upon the principles of beneficence, nonmaleficence, patient autonomy, and particularly the concept of double effect. The pragmatic foundation of pain management begins with a complete assessment, which incorporates "WILDA" (words, intensity, location, duration, aggravating/alleviating factors) and considers the components of total pain: physical, emotional, social, and spiritual pain. Opioids are the pharmacologic *sine qua non* of pain management in life-limiting illness and should be prescribed based on the severity of pain, considering the functional and psychological significance of that severity. Numerous misunderstandings present a barrier to effective pain management. These misconceptions include the idea that opioids are highly addictive, that dependence or tolerance are forms of addiction, that respiratory depression is common with opioids, that opioids have a narrow therapeutic range, and that opioids are ineffective by mouth and cause too much nausea. In reality, opioids are the safest and most effective pain medicine for most moderate to severe pain in most patients. Aspects of basic opioid pharmacology, such as dosage, route of administration, rotation of drugs, and the avoidance of toxicity and complications, should be considered when initiating and maintaining therapy. Failure to pay attention to the basic rules can lead to errors in opioid management.

> We all must die. But that I can save him from days of torture, that is what I feel is my great and ever new privilege. Pain is a more terrible lord of mankind than death itself.
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> —Albert Schweitzer, MD, physician, humanitarian, theologian (1)

As physicians, we understand that we cannot cure every patient we see. At best, we delay inevitable mortality. The relief of pain and suffering, however, is always within our capabilities, yet our endeavors to do so are not without uncertainty and misunderstanding, both within the profession and without.

Consider the recently publicized case of Anna Pou, MD, the chief of the head and neck surgery service at Louisiana State University School of Medicine. During Hurricane Katrina, Dr. Pou stayed behind in New Orleans to tend to her patients when others fled. For her sacrifice and dedication in serving humanity in the most dire of circumstances, she has now been indicted for murder, along with two nurses, Lori Budo and Cheri Landry. The local district attorney in New Orleans has accused her of administering lethal doses of narcotics to frail, elderly patients who could not be evacuated. I do not personally know Dr. Pou, but I have read her resume and know many physicians like her—physicians dedicated first to the good of their patients, with their own needs taking a subservient role. Dr. Pou is not Dr. Kevorkian, and it strains credulity to claim that a physician of her obvious dedication and stature would intentionally kill a patient, as some are suggesting. Clearly there is misunderstanding on the part of other health care professionals at the hospital where she practiced and misunderstanding on the part of the district attorney. Her case points to the need to increase education about practical and ethical issues related to opioid use, particularly in life-limiting illness, both within the healing professions and among the broader public.

This article reviews basic pain assessment, including the concept of total pain; the ethical foundation of pain management strategies; distinctions between tolerance, dependence, and addiction; and a rational, evidence-based approach to analgesia with an emphasis on opioid pharmacology.

CASE STUDY: ASSESSMENT

I would like to introduce the topic with a recent case. A 68-year-old woman of Southeast Asian descent came to Baylor University Medical Center from Atlanta to seek a second opinion on treatment of locally advanced breast carcinoma. On presentation at Baylor, she had a large malodorous ulcer of the chest wall accompanied by massive lymphedema of the right arm. During her first palliative care visit, she reported a chief complaint of severe pain that had been continuous for months. She described this pain as a constant burning with intermittent

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twitching. She located the pain across the right anterior chest wall, axilla, and right upper arm. She rated her current pain as 4 on a pain scale of 0 to 10 (with 10 being the most severe), and this was 2 hours after taking a 10-mg hydrocodone/325-mg acetaminophen tablet. Her best pain in the past 24 hours and past several months was a 3 on the 10-point pain scale, and her worst pain in the previous 24 hours was a 9. She had spent many hours in the past few months with pain at a 10.

Upon further questioning, she indicated that exposure to heat and movement of her right arm exacerbated the pain. This meant that she could no longer cook for her family or perform other tasks she wanted to do as a mother and wife. These limitations sapped her sense of purpose and worth in life. They also meant that she required assistance with simple tasks such as dressing. After a lifetime of helping others, she found this very unsatisfactory and demeaning. She admitted to a feeling of depression as well as spiritual distress, which I will comment on later. She had no major associated symptoms otherwise.

ASSESSMENT OF PAIN

The case report illustrates several of the elements involved in the assessment of pain. The first questions to ask have been summarized with the acronym WILDA: words to describe pain, intensity on a scale of 0 to 10, location/radiation pattern, duration, and aggravating/alleviating factors. When rating pain, it is important to find out what number the patient finds acceptable and unacceptable. Most patients indicate that pain at level 3 or 4 can be tolerated. Pain scores higher than that are not acceptable to most patients, and if you ask if they would like their pain to improve, they will answer yes. WILDA questions are easy to use, and thus it is somewhat surprising how often answers to those questions are not documented in patient charts, even for patients with severe pain. We would not imagine treating hypokalemia or hyperkalemia without measuring the degree of abnormality. How do we think we can treat pain if we do not measure and record the degree of abnormality?

Beyond the WILDA characteristics of pain, it is also helpful to consider whether physical pain is primarily nociceptive or neuropathic, as this will influence therapeutic interventions. Nociceptive pain involves stimulation of intact nociceptors. The injury is apparent. This kind of pain is often described as dull, aching, or throbbing. Nociceptive pain may be somatic or visceral. Somatic pain tends to be fairly well localized and the tissue injury is usually obvious, as with this patient. Visceral pain is more poorly localized and often has a spasmodic or colicky quality as well.

Neuropathic pain is caused by damage to neural tissues, either central or peripheral, and the injury is often not apparent to the health care professional examining the patient. This type of pain may be described as stinging, shooting, burning, tingling, or a cold painful sensation. The intermittent twitching and burning of this patient's pain suggested a neuropathic component as well.

As part of pain assessment, especially in the setting of life-limiting illness, physicians must also consider *total pain,* a concept articulated in the modern era by Dr. Cicely Saunders (2). Physical pain represents only one type of pain we may have; as important as it is, we are derelict in our duty as healers if we do not also assess other physical symptoms and the components of total pain. Many other significant physical symptoms, such as dyspnea, nausea, fatigue, and sleep disorders, contribute to the overall symptom burden of a patient with advanced disease. But beyond these additional physical symptoms, a patient may experience emotional pain (manifested as depression, anxiety, grief), social pain (presenting with isolation, economic hardship, fear for one's survivors), and spiritual pain (feelings of despair, loss of hope, questions about purpose and meaning, relationship with God or the transcendent). These different components of total pain are often highly interdependent. Successful treatment of one often requires treatment of the others, and as with treatment of physical pain, a component of total pain cannot be treated if it is not appropriately assessed. Members of Baylor's palliative care team look for and assess total pain. This process is time consuming but one of the most important services our team provides patients as part of comprehensive evaluation and management.

To address total pain, interdisciplinary services can be most beneficial. We are fortunate at Baylor University Medical Center to have numerous resources available to assist with pain management, including formal pain management consults, formal palliative care consults, and the ad hoc assistance of specially trained palliative care nurses, a pain management nurse, and a palliative care pharmacist. Physicians may access pastoral care practitioners for assistance with patients' spiritual issues. Complementary therapy is also available, including breathing techniques for patients with dyspnea, massage therapy, and aromatherapy for patients with nausea. Everyone on Baylor's interdisciplinary palliative care team has been cross-trained so that they can at least begin answering questions concerning pain management, death and dying, advanced care planning, and related topics.

Returning to the case at hand, I asked the patient how much pain medication she was taking and whether she had told her physicians that she was still in pain. She indicated that the physician had ordered one or two 10-mg/325-mg Norco pills every 6 hours, but she had taken only two to four pills in the past 24 hours—half what was prescribed. She estimated that the pain relief she achieved lasted only 1 to 2 hours; thus, on most days she spent most of her waking hours in severe pain. One reason she did not take more pain medicine to deal with this pain was her belief that she would become addicted. In addition, she thought God wanted her to suffer and was punishing her. As she prayed about her circumstance in life, she had come to the conclusion that perhaps she deserved to suffer or perhaps there was a higher purpose to her suffering. When I asked how she was trying to cope with this suffering, she reported, "I must bear my suffering like Jesus on the cross."

This scenario of treatable yet ineffectively treated physical pain (as well as total pain) should raise multiple questions. Was the patient's current pain management either ethically or physiologically acceptable? If not, what were the barriers to effective pain management, in particular for a patient like her with severe pain and advanced life-limiting illness?

I propose that there are three basic barriers to effective pain management: unjustified ethical concerns; misconceptions about dependency, addiction, and tolerance with opioid use; and misunderstandings about basic opioid pharmacology.

THE ETHICS OF PAIN MANAGEMENT

Principle-based ethical analysis is easily applied to pain management. Consider the principle of *beneficence* applied in the setting of pain: it is good to relieve pain. We all want our pain relieved. The principle of *nonmaleficence,* or avoiding harm, is also easily applicable, since pain is harmful emotionally, socially, spiritually, and even physiologically. Some argue that opioids themselves are harmful; however, serious harm is rare if the drugs are used properly, particularly in the setting of life-limiting illness. Applying the principle of *autonomy* in this setting, we might note that patients have a right to be self-governing and that patients cannot exercise their autonomy if they are not well educated about their options—in this case, the option of better pain control. In addition, patients cannot exercise their autonomy if they are in such severe pain that both their body and their soul are in shackles. In the case study, not only was the patient's physical autonomy restricted by her pain, but her spiritual and emotional autonomy were crushed by the long-standing burden of total pain and the unanswered questions total pain had left in her life.

Moving beyond the application of basic ethical principles, perhaps the most important ethical concept related to pain management in advanced disease is that of *double effect.* This principle justifies most of what we do in medicine, although it is most frequently referred to in the setting of symptom management near the end of life. The basic rules for using double effect to justify our moral actions are as follows. First, the treatment—in this case, a high dose of opioid—must be the only means to meet the end desired, the cessation of intractable pain. Second, the physician must intend only the good effect, in this case the relief of suffering. Third, the good effect must, in our moral analysis, outweigh any unintended bad effect. Such a bad effect might be an earlier death than might otherwise occur, although that is in fact unlikely. Finally, the bad effect (possible earlier death) should not be the means to the good effect (pain relief). If we were to allow the bad effect of an earlier death to be the sole means to the good effect of pain relief, then we would not titrate opioids to pain relief but simply give the patient a lethal dose of potassium—something that should not be done!

On our palliative care service and other palliative care services, very high doses of opioids are frequently used without patients dying shortly after administration of the drug. On the contrary, there are many times when we thought a patient near the end of life and in severe pain would die during or following the administration of high doses of opioids and instead the patient lingered much longer than expected. My own experience suggests that decreasing severe pain and other symptoms of dying may sometimes prolong life, perhaps due to the lowered physiologic stress when the patient is no longer in severe pain.

PSYCHOSOCIAL MISCONCEPTIONS ABOUT OPIOIDS

Misconception: Opioids are highly addictive

One reason the patient in our case study was taking only half the prescribed dose of pain medication was a fear of addiction. The word *addict* conjures up negative images in most people's minds and is thus a concept worth exploring. The word comes from the Latin *addictus,* which means to be devoted to; the Latin word had a positive connotation. In our time, the word has lost that positive meaning. Behaviorally, addiction is characterized by impaired control over drug use, compulsive use, use despite harm, craving, and loss of interest in pleasurable activities. If you think about cancer patients, burn patients, or for that matter patients with chronic arthritis experiencing severe debilitating pain, they don't have impaired control over the use; they need the drug to relieve their pain. If we fail to understand the severity of the patient's pain, we may confuse addiction with pseudo-addiction, which is a drug-seeking behavior because pain is not treated well.

Moving beyond the linguistic analysis of addiction, the reality is that opioids are rarely addictive in the setting of life-limiting illness. Substantial information in the peer-reviewed literature backs up this statement. For example:

- In 1980, Porter and Jick reported on a prospective study of 12,000 hospitalized patients who received at least one opioid preparation for moderate to severe pain. They found only four reasonably well-documented cases of addictive behavior (3).
- In 1981, Kanner and Foley noted that the medical use of opioids rarely leads to drug abuse or to iatrogenic opioid addiction among cancer patients (4).
- In 1982, 181 health care professionals with an average of 6 years of experience who worked at 93 burn units and cared for at least 10,000 hospitalized patients reported no case of addiction in patients treated for burn pain (5).
- In 1992, Schug et al reported only one case of addiction among 550 cancer patients who experienced pain and were treated with morphine for a total of 22,525 treatment days (6).
- In 1992, Zenz et al reported no incidents of serious toxicity or addiction among 100 patients with diverse pain syndromes who received narcotics for prolonged periods (7).

I do not want to leave the impression that addiction to opioids is never a problem. It does happen but not significantly in the setting of advanced life-limiting illness. I worry more about a family member diverting a terminally ill patient's opioids than I worry about the patient diverting and abusing the drugs. Even in the latter case, in the setting of a terminal disease, it is better for the patient to go to the grave an "addict" than in severe pain. Death is going to occur, but pain does not have to.

Misconception: Physical dependence on opioids is the same as addiction

Dependence on opioids occurs and is a physiological neuroadaptation. If patients take narcotics for any length of time for chronic pain, they will become dependent on them, and abrupt withdrawal may lead to an abstinence syndrome. This

withdrawal does not mean that patients were addicted but only that they were dependent, just as patients may become dependent on other pharmacologic agents.

The Schug et al study cited above addressed this issue of dependence with opioids. Among their 550 cancer patients treated with morphine for 22,525 treatment days, physical dependence posed no practical problem (6). An increase in morphine dosage was usually associated with progression of disease, not dependence.

Misconception: Tolerance is related to dependence or addiction

Tolerance has been defined as "a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time" (8). The diminution over time may be related to either side effects or efficacy. In opioid use, nausea is fairly common with drug initiation but almost always goes away. Some patients do not want to take opioids because of their initial experience with nausea, which they sometimes refer to as an "allergy." They require reassurance that this nausea will pass or can usually be resolved with antinauseant medications. Reduced efficacy due to tolerance is usually not clinically significant with chronic dosing. Although tolerance to the pain-relieving effects of narcotics can occur, physicians should suspect disease progression when a previously effective dose no longer appears to work.

PRACTICAL MISCONCEPTIONS ABOUT OPIOIDS

Health care professionals and the public have numerous practical misconceptions about opioids. Physicians and nurses have an obligation to avoid these misconceptions and help others move beyond them. Failure to abandon our misconceptions about opioids inevitably leads to undertreatment of severe pain—because the doctor fails to order the medication in an adequate dose, the nurse fails to administer the dose, or the patient fails to take the dose.

Misconception: Respiratory depression is common

Occasionally physicians order very appropriate doses of narcotics and find that the nurses do not administer them for fear that the patient will stop breathing. The reality is that respiratory depression with opioids in the setting of life-limiting illness is rare. Bruera and MacEachern conducted a placebo-controlled crossover study of opioids in cancer patients with dyspnea and documented efficacy without significant respiratory depression (9).

Pain is a potent stimulus to breathe, and when pain is removed, respirations may slow. The patient may drop from 24 breaths per minute to a relaxed 10 or 12 breaths per minute. If respiratory arrest were to occur, it would normally be preceded by loss of consciousness. If the respiratory rate drops to less than 6 or 8 breaths per minute, clinicians may consider holding the opioid dose and seeing if the effect wears off. In patients with life-limiting terminal illness, naloxone use should be rare. If it is used, 1 ampule of 0.4 mg should be diluted in 10 mL saline, and 1 mL of the mixture should be given every 5 minutes until the effect is partially reversed.

Jennings et al have demonstrated that opioids are also safe and effective for the treatment of dyspnea or pain in patients with chronic obstructive pulmonary disease and heart failure (10). Opioid dosages for treatment of dyspnea are low, typically 1 to 2 mg of intravenous morphine as often as every hour if needed depending on circumstances.

Misconception: Opioids have a narrow therapeutic range

Opioids actually have a very broad therapeutic range. In fact, opioids are the safest and most effective pain medicine for most moderate to severe pain in most patients with both nonterminal and terminal diseases. They are much safer than nonsteroidal anti-inflammatory medications, which often lead to bleeding, renal insufficiency, or other problems.

Unlike other pain relievers, opioids have no ceiling effect. Patients do not achieve better pain relief with 8000 mg a day of acetaminophen than with 4000 mg. In addition to this ceiling effect in terms of efficacy, acetaminophen leads to significant, even life-threatening toxicity at higher dosages. Opioids are quite different. Some patients require small doses of 2 mg of oral morphine every 4 hours to achieve pain relief; others may need doses as high as 200 mg or more. Despite the well-understood pharmacology of opioid dosing, some physicians and nurses have an idiosyncratic, nonscientific ceiling above which they will not prescribe or administer these drugs. This approach harms patients.

Misconception: Opioids are ineffective by mouth and cause too much nausea

Some believe that opioids must be given parenterally because they don't work when ingested orally. In fact, opioids are very effective orally, but because they undergo first-pass metabolism in the liver, dosages will often need to be adjusted. For example, oral morphine is about one third as potent as parenteral morphine, so if a patient's pain is well controlled on 10 mg of intravenous morphine every 3 hours, the equivalent oral dose would be 30 mg.

While nausea can be a problem, as mentioned earlier many patients develop a tolerance to it. No nonopioid pain reliever will be effective for pain rated a 9 or 10 on the pain scale, so we need to encourage patients to work through this side effect when possible. Some physicians recommend the routine administration of an antinauseant when initiating opioid therapy. I have not found that necessary unless a patient reports a prior reaction to an opioid. In that case, an antinauseant along with the opioid is definitely indicated.

Misconception: Substance abusers should not be given opioids

The palliative care or ethics consultation service receives occasional referrals related to pain relief for substance abusers. Sometimes physicians do not want to order anything other than acetaminophen for these patients' pain because of current or prior substance abuse. This is a difficult area, but the reality is that substance abusers also have terminal or life-limiting illnesses. They must be treated with compassion. If they are terminally

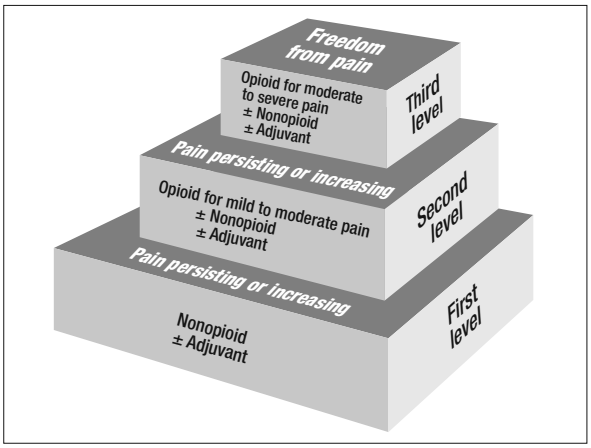

Figure 1. The three-step pain relief ladder developed by the World Health Organization. The first level is appropriate for mild pain (1 to 3 on the 0–10 pain scale); the second level, for moderate pain (4 to 6); and the third level, for severe pain (7 to 10).

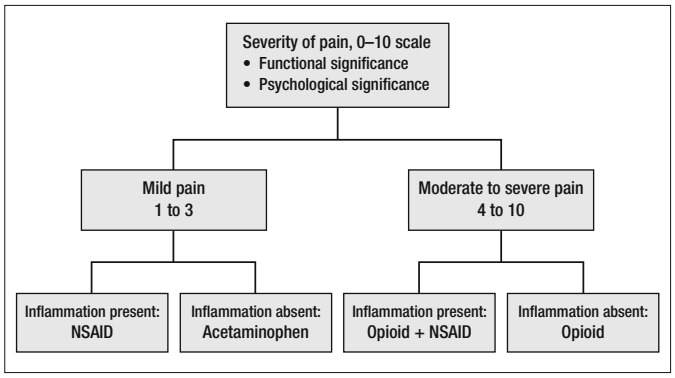

Figure 2. An alternative approach to pain treatment that categorizes pain by severity and inflammation. Adjuvants are appropriate at all times as indicated by the condition. NSAID indicates nonsteroidal anti-inflammatory drug.

ill, I believe their substance abuse history should not disqualify them from effective pain management. Such patients are often incredibly tolerant of opioids, and they often need large doses in the setting of a terminal illness. It can be useful to consult with pain specialists, addiction specialists, or psychiatrists for these patients. Strict dosing protocols and written contracts should be considered with substance abusers.

BASIC OPIOID PHARMACOLOGY AND USE

As explained earlier, to use opioids effectively, the physician must first know the patient as a person and conduct an appropriate pain assessment. The physician must also be cognizant of and avoid the barriers I have mentioned. Finally, the physician must know basic opioid pharmacology: the correct dosage, correct route of administration, rotation of drugs, ways to monitor and prevent toxicity, and ways to preempt complications.

Basic pharmacology

The peak effect of opioids depends on the route of administration. Given intravenously, opioids peak at about 10 minutes; given subcutaneously, at 30 minutes; and given orally, at 60 minutes (or 120 minutes for methadone). For all routes of administration, the half-life at steady state is 3 to 4 hours, with the exception of methadone, and steady state is usually achieved at about 24 hours.

The duration of immediate-release oral opioids is typically 3 to 4 hours. Therefore, it does not make sense to order hydrocodone with acetaminophen every 6 hours, as was done in our case study. The duration is somewhat shorter with parenteral boluses. Sustained-release drugs have a duration of about 12 hours for MS Contin and OxyContin or about 24 hours for Avinza. Kadian is supposed to be prescribed every 12 to 24 hours but probably lasts about 16 to 18 hours.

There are some concerns with morphine clearance, although they are rarely a significant issue in terminally ill patients. In the liver, morphine is converted to both an inactive and active metabolite. The active metabolite, M6G, is excreted by the kidneys, so when the kidneys shut down, this metabolite may accumulate and cause toxicity. When patients are dehydrated or are experiencing renal or hepatic failure, physicians should consider increasing the dosage interval and/or decreasing the dosage size. If oliguria or anuria develops, physicians should consider stopping the routine dosing of morphine in favor of as-needed dosing or switching to methadone or fentanyl. I try to avoid hydrocodone and codeine in patients with chronic liver disease because of uncertainty about how well these agents will be metabolized to the active pain relievers hydromorphone and morphine, respectively, in any given patient.

Initiating opioids

The severity of the pain should be considered when initiating opioids. A patient with a pain score of 9 should not be started on a 5/325 Norco pill. That pill will not be strong enough, and the patient will require higher dosages. The World Health Organization developed a three-step pain ladder to help guide the choice of drugs based upon the severity of pain *(Figure 1)*. Another approach is to categorize pain based on severity and the presence or absence of inflammation *(Figure 2)*. Whether one uses the pain ladder or an alternative classification system, it is important to consider the functional and psychological significance of the pain. Some patients will say that their pain score is a 2 or 3. However, you might note that they are not getting out of bed. If you inquire, you might learn that their pain increases to a 10 if they do so. Such a patient is functionally crippled by pain and should be treated more aggressively than the reported pain score of 3 would warrant.

Patients' age and weight should be considered when initiating opioids. Older and smaller patients may need lower dosages. In addition, transdermal fentanyl may not be well absorbed in very cachectic patients with little body fat, whereas it is absorbed more rapidly in febrile patients. Physicians should also consider patients' prior analgesic use and experience since tolerance can occur. The presence of hepatic and renal disease is another consideration.

Typical opioid therapy is initiated with immediate-release opioids, such as hydrocodone, morphine, hydromorphone, and oxycodone. These drugs should be given orally if possible. Standard starting dosages are 5 to 20 mg of morphine or hydrocodone every 4 hours; 5 to 15 mg of oxycodone every 4 hours;

and 1 to 4 mg of hydromorphone every 3 hours for moderate to severe pain. The more severe the pain, the higher the initial oral dose the patient is likely to need. Very few physicians start with a full hydrocodone dose of 20 mg. Instead, I often see orders for one Norco 5/325 for patients who have rated their pain as a 9 or 10. Typically, such dosages will prove inadequate for patients with severe pain near the end of life.

Regardless of the starting dose, in the setting of terminal illness in particular, the dose can be titrated upward very rapidly, giving about half of the 4-hour dose for breakthrough pain at the drug's peak. Remember that the peak effect of an oral dose occurs after 60 minutes and of a parenteral dose, after 10 to 30 minutes. Thus, if the patient does not experience relief at these peak times, additional dosages may be given at that time when pain is severe and you are trying to control it. Remember to exercise caution with extra dosages of hydrocodone/acetaminophen combinations because of acetaminophen toxicity. I typically stay away from opioid/acetaminophen combinations in the setting of severe pain because of my concern that the patient, desperate with pain, will take more medicine than I have prescribed. These patients are better off with morphine or hydromorphone.

Maintenance therapy

Once the 24-hour dose is fairly well established, physicians should switch the patient to a sustained-release agent, such as MS Contin, OxyContin, Avinza, or Kadian. For example, if a patient is stable on immediate-release morphine at 20 mg every 4 hours, for a total of 120 mg every 24 hours, the appropriate sustained-release dose would be MS Contin at 60 mg every 12 hours. For breakthrough pain, 10 mg of immediate-release morphine every 1 hour as needed can be ordered. This dosage is roughly equivalent to 50% of the dose given every 4 hours or 10% of the dose given every 24 hours.

When a patient does not seem to be responding to escalating dosages of a particular opioid, consider other factors such as spiritual or emotional pain as a cause. In addition, the patient may benefit from a switch to a different opioid.

Opioid options

Hydrocodone. Hydrocodone is generally equipotent with morphine. In the USA, hydrocodone is available only in combination with acetaminophen, ibuprofen, or the cough suppressant homatropine. At Baylor University Medical Center, hydrocodone is available combined with 325 mg of acetaminophen, but in the community the combination is available with 500, 660, and 750 mg of acetaminophen. With such high acetaminophen doses, patients can develop major hepatotoxicity. The other combinations are 200 mg of ibuprofen with 7.5 mg of hydrocodone and 1.5 mg of homatropine with 5 mg of hydrocodone.

Oxycodone (OxyFast, OxyIR, OxyContin). Oxycodone is more potent than morphine (with ratios of about 1.5:1) and may be less likely to cause hallucinations and nightmares, although I rarely see either complication in my patients on morphine. The drug is available in tablet form (at 5, 15, and 30 mg) and liquid form (5 or 20 mg/mL). Typical immediate-release doses of oxycodone are in the 5 to 15 mg range, but even 30 mg may be given every 4 hours. The sustained-release product, OxyContin, is available at standard strengths of 10, 20, 40, or 80 mg every 12 hours. Although there have been extensive reports of OxyContin abuse, particularly in the Appalachians, it is a perfectly good drug.

Hydromorphone (Dilaudid). This drug is available in several immediate-release forms: as a tablet (2, 4, 8 mg), liquid (1 mg/mL), rectal suppository, and parenteral injection. Hydromorphone comes premixed with acetaminophen, although I personally avoid that combination. It should generally be started at a dose interval of every 3 hours because of its somewhat shorter half-life. The potency of hydromorphone is about 4 or 5 times that of morphine; thus, 10 mg of morphine is equivalent to about 2 or 2.5 mg of hydromorphone.

A sustained-release version of hydromorphone called Palladone was available in the USA for a short period. Although we found it to be an excellent product for the patients we see in palliative care, it was pulled off the market after several patients mixed it with alcohol and had severe side effects. I believe this was an overzealous reaction by the regulatory agencies, for if other opioids are mixed with alcohol, problems will arise as well. Palladone is still available in Europe, where drug policy in general is a bit more sensible.

Methadone can be very effective when other narcotics are failing. It is probably the opioid of choice for patients with severe neuropathic pain or renal failure. Other clinical indications include persistent or severe adverse effects from morphine or other narcotics and failure of morphine and adjuvants to relieve pain. The drug is inexpensive and is appealing on cost-control grounds as well. Despite having several potential advantages, the drug has atypical and somewhat less predictable pharmacokinetics, and even those of us who are more experienced with the drug use it with a bit of trepidation. Methadone is a racemic mixture: one stereoisomer serves as an *N*-methyl-D-aspartate receptor antagonist, and the other isomer serves as an opioid mu-receptor agonist. It has an extraordinarily long terminal half-life of about 190 hours, which does not correlate with its analgesic effect of between 6 and 12 hours. Published conversion guidelines specific to methadone should be consulted before using this drug for a patient with severe pain. A pain management nurse specialist or pharmacist could also be consulted.

Options for routes of administration

Opioids can be delivered in several ways, including orally, enterally through feeding tubes, rectally, parenterally, and intraspinally. Two other routes are transmucosal, for immediate-release dosing, and transdermal, for sustained-release dosing.

Transmucosal. Roxanol is a highly concentrated oral morphine solution, and OxyFast is a highly concentrated oral oxycodone solution. They are probably not absorbed across the buccal membrane but work through trickle down to the gastrointestinal tract. Dosages can be easily titrated. There is also a hydromorphone solution suitable for placement under the tongue with trickle-down absorption. Actiq is an orally

dissolving dose of fentanyl in a "lollipop" form. It dissolves in about 15 minutes and is available in dosages ranging from 200 to 1600 mcg per lollipop. It is absorbed across the buccal membranes. While it is a nice product, it is expensive. In my judgment, it is best reserved for use in anticipation of acute pain exacerbations, such as before wound care or perhaps before physical therapy.

Transdermal. Fentanyl patches (Duragesic) begin working 18 to 24 hours after they are applied and last for 72 hours. Dosages of 12.5, 25, 50, 75, and 100 mcg an hour are available. In terms of equivalency to other narcotics, 100 mg of oral morphine per 24 hours is equivalent to 25 to 50 mcg an hour of fentanyl. Although patients may use more than one patch at a time provided they have adequate skin surface area, the transdermal route is not cost-effective if patients need three or four patches simultaneously. In those cases, a different narcotic should be chosen. As a general rule, the patches are not appropriate for opioid-naive patients. As with other sustained-release products, provisions for breakthrough pain with an immediate-release oral or parenteral opioid must be made. I try to avoid using fentanyl patches in combination with other sustained-release opioids. As noted earlier, with the patches, absorption of fentanyl is increased in febrile patients and decreased in cachectic patients. When switching back to oral medicine, the oral drug should be started 12 to 18 hours before the patch is removed. Finally, transdermal fentanyl patches should not be cut.

Adverse effects

The most common adverse effect of opioids is constipation. This is the only adverse effect to which patients do not develop tolerance. It is very important to start an osmotic or stimulant laxative when opioids are initiated. Fiber products will compound the problem of opioid-induced constipation. Other common adverse effects such as dry mouth, nausea/vomiting, sedation, pruritus, urticaria, and sweating are easily managed. Nausea often spontaneously resolves or can be easily treated with antinauseant medications. Excessive sedation may be treated with small dosages of a stimulant such as dextroamphetamine or methylphenidate. Uncommon adverse effects include bad dreams/hallucinations, dysphoria/delirium, myoclonus/seizures, respiratory depression, and urinary retention. These more serious adverse effects often warrant a change in therapy.

Common errors in opioid prescribing

There are five common errors in opioid management to be aware of and avoid.

1. *Failure to accurately assess the pain.* It is not enough to ask one question about pain and then move on to other topics; physicians must get a complete picture of the patient's pain. As with any other problem we treat, if we do not assess the problem correctly, we are not likely to treat the problem effectively.

2. *Errors in dosage and timing.* Typically the dose ordered is too small and the dosing interval is too great. Another problem is unnecessary complexity, such as the use of multiple opioids in the same patient. Sometimes there is too much flexibility in the order, leading to variable interpretations between different nurses. For example, if an order reads, "Morphine 2 to 10 mg by intravenous push every 4 to 6 hours as needed for pain," one nurse might give 2 mg every 6 hours, another nurse might give 10 mg every 4 hours, and another nurse might not give any if she felt the pain was not severe enough. All three would technically be following the order correctly, and yet on a 24-hour basis the total morphine dose would vary from 0 to 60 mg. A better order might read, "Morphine 5 mg by intravenous push every 3 hours as needed for moderate or severe pain graded by the patient as 4 or worse on the pain scale." One of the first things we often do in palliative care consults is to calculate the total narcotic dose, convert the patient to a single long-acting agent if possible, and clear up confusion in the nurse's mind as to what level of breakthrough pain is to be treated and at what time interval.

3. *Errors in opioid conversion calculations.* If you are going to be doing complex opioid conversions, ask the pharmacist to double-check your calculations. I've seen problems with patients being both underdosed and overdosed due to incorrect conversion calculations.

4. *Failure to recognize and treat toxicity.* It is worth repeating that any time we write a prescription for an opioid, we should simultaneously write a prescription for an osmotic or stimulant laxative, unless the patient has diarrhea. Make certain that an antinauseant is available. If the patient has a history of narcotic-induced nausea, start the antinauseant prophylactically. If excessive daytime drowsiness is a problem, consider a psychostimulant such as dextroamphetamine.

5. *Inadequate use of adjuvants.* This problem occurs particularly with inflammatory pain or neuropathic pain. When used correctly, adjuvants may have an opioid-sparing effect. If inflammation is present, nonsteroidal anti-inflammatory drugs are appropriate. Steroids may be helpful in a number of circumstances. Numerous adjuvant agents are now available for neuropathic pain.

CASE STUDY: TREATMENT

Returning to the case study, our 68-year-old patient with locally recurrent breast cancer was receiving 20 to 40 mg of hydrocodone every 24 hours and continued to have severe pain. Several steps were taken to improve her pain.

First, I educated the patient and the family about opioid misconceptions. The goal was to get them past the idea that she was going to become addicted or that her disease and pain indicated that she was a bad person and deserved to be in pain. She had come to the conclusion that God was punishing her for a wrong she had done in her life. I explored that issue gently with her, suggested a more forgiving interpretation of the deity, and prescribed a book, *Why Bad Things Happen to Good People,* for her spiritual distress. There are other useful books to consider as part of cognitive therapy for patients with advanced illness. I often recommend Victor Frankl's *Man's Search for Meaning.*

I prescribed a long-acting opioid—in this case a 25-mcg/hr fentanyl patch every 3 days—that would not require her to pay much attention to timing. I explained the delay in the drug's effect and also the sedation that might occur when she first

started using the patch. I left her on the Norco 10/325 for breakthrough pain because she had already purchased it, and I prescribed a daily stimulant laxative. Finally, I prescribed a medication for her neuropathic pain and depression, in this case duloxetine 30 mg daily. The patient reported a marked improvement in her physical pain within 24 hours. She did experience increased somnolence, but that wore off with time and medication adjustments. By the following week, the patient's attitude was much better. As her physical symptoms improved, her emotional and spiritual distress began to improve as well, even though she remained terminally ill.

CONCLUSION

Although an article of this short length cannot do full justice to the topic of pain management in life-limiting illness, it is hoped that it reminds us of the need for better attention to pain control and the possibility of real improvement in total pain control. Sir William Osler stated that the goal of physicians is "to cure sometimes, to relieve often, to comfort always." Careful attention to the science and art of pain management and comfort is every bit as important as cure, for as long as we are mortal, cure of the human condition must ultimately fail. Death is inevitable; suffering is not.

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